Nanomicelle formulation modifies the pharmacokinetic profiles and cardiac toxicity of daunorubicin.

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Public Summary:
Daunorubicin formulated in nanometer-scale micelles has favorable drug distribution in patients, signficantly reduced toxicity to heart and improved anti-tumor activity.

Scientific Abstract:
Background: Treatment with daunorubicin (DNR) in acute myeloid leukemia is moderately effective and associated with significant side effects, including cardiac toxicity. We recently developed a nanomicellar formulation of DNR that specifically targets acute myeloid leukemia stem cells. Materials & methods: Pharmacokinetics analysis of free DNR, DNR in nanomicellar formulations was performed in Balb/c mice and Sprague-Dawley rats. Histochemical staining, caspase 3/7, troponin and creatine kinase MB isoenzyme were used to assess toxicity. Results: Compared with free DNR, the nanomicellar formulations of DNR had less cardiotoxicity as evidenced by milder histopathological changes, lower caspase 3/7 activity in heart tissue ($p = 0.002$), lower plasma creatine kinase MB isoenzyme ($p = 0.002$) and troponin concentrations ($p = 0.001$) postinjection. The area under curve concentration of DNR in micelles increased by 31.9-fold in mice ($p < 0.0001$) and 22.0-fold higher in rats ($p < 0.001$). Conclusion: Leukemia stem cell-targeting micelles dramatically change the pharmacokinetics and reduce the cardiac toxicity of DNR, which may enable improved DNR-based treatment of acute myeloid leukemia. Original submitted 24 January 2014; Revised submitted 28 February 2014.